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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,066	ALPAR ET AL.	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,11-22,36 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,11-22,36 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 8, 2005 has been entered.

Amendment Entry

2. The amendment filed August 8, 2005 has been entered. Claims 1, 3, 6, 16 and 21 have been amended. Claims 2, 7-10, 23-35 and 38-39 have been cancelled. Claims 1, 3-6, 11-22 and 36-37 are under consideration in this office action.

Withdrawal of Rejections

3. The following rejections have been withdrawn in view of applicants' amendments and arguments:

a) The rejection of claims 1-2, 4-6, 11-12, 16, 18-19 and 37 under 35 U.S.C. 102(b) as being anticipated by Illum (WO 97/20576);

b) The rejection of claims 13-15,17 and 20-22 under 35 U.S.C. 103(a) as being unpatentable over Illum in view of Eyles et al;

c) The rejection of claim 3 under 35 U.S.C. 103(a) as being unpatentable over Illum in view of Kotze et al;

d) The rejection of claims 22, 36 and 38 under 35 U.S.C. 103(a) as being unpatentable over Illum and Eyles et al., and further in view of Kotze et al;

e) The rejection of claim 23 under 35 U.S.C. 103(a) as being unpatentable by Illum (WO 97/20576) in view of Eyles et al;

f) The written description rejection of claims 38-39 under 35 U.S.C. 112, first paragraph; and

g) The new matter rejection of claims 38-39 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Response to Arguments

4. Applicant's arguments with respect to claims 1, 3-6, 11-22 and 36-37 have been considered but are moot in view of the new ground(s) of rejection.

New Grounds Of Objection and Rejections

Claim Objections

5. Claims 18-19 and 36 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 18-19 are drawn to the composition being adapted for intranasal or parental administration, however this adaptation does not further limit the composition. This adaptation does not add more components to the composition, therefor the claims are objected to. Furthermore, claim 36 is drawn to the composition that has trimethyl chitosan distributed throughout the particles including the surface, however again the claim does not add any additional components to the composition therefore the claim does not further limit the composition and appropriate clarification is required to overcome the objection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Kotze et al., (International J. of Pharm., 1997).

The claims are drawn to a pharmaceutical composition comprising a polycationic carbohydrate wherein the polycationic carbohydrate is the water soluble alkylated trimethyl chitosan or a salt derivative thereof.

Kotze et al., teach N-trimethyl chitosan chloride as a potential absorption enhancer across mucosal surfaces. Chitosan is a polycationic polymer with numerous applications (page 1197). Chitosan is highly available at low cost, highly biocompatible, biodegradable and easily chemically modified (page 1197). Chitosan has gel-forming properties and can be used as a drug carrier in hydrocolloids (page 1197). Chitosan is also used as a constituent in polymeric matrix systems, microspheres and microcapsules for sustained release of water-soluble drugs (page 1197). The mucoadhesive properties of chitosan and its ability to act as an absorption enhancer has led to its use as a coating material for multilamellar liposomes (page 1197). Thus the water-soluble chitosan derivative N-trimethyl chitosan chloride affects the permeability of cells and increases the transport of large hydrophilic compounds such as peptide drugs (page 1197).

Thus Kotze et al., teach a pharmaceutical composition comprising water soluble alkylated trimethyl chitosan or a salt derivative thereof.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 3-4, 6, 11-18 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kotze et al., (International J. of Pharm., 1997) in view of Eyles,

The claims are drawn to the pharmaceutical composition comprising a trimethyl chitosan and a combination of a V and F1 antigen of *Yersinia pestis* wherein the composition further comprises particles.

Kotze et al., has been discussed above as teaching a composition comprising trimethyl chitosan however Kotze et al., do not discuss a composition further comprising the combination of the V and F1 antigen of *Yersinia pestis* and compositions which comprise microspheres.

Eyles et al., teach intra-nasal administration of poly-lactic acid microspheres co-encapsulated with *Yersinia pestis* subunits that confer protection from pneumonic plague in mice. *Yersinia pestis* has a capsule that surrounds the bacterium and contains a protein-polysaccharide complex, which was termed the F1 subunit (page 698). The F1 antigen confers resistance to phagocytosis (page 698). Similarly, the secreted V

antigen exerts local anti-inflammatory effects via modulation of tissue cytokine levels (page 698). Both F1 and V antigens are protective, although there is an additive effect in the combination (page 698). Encapsulation of antigenic material within microparticulate polymeric carriers, such as poly-DL-lactide (PLA) microspheres serves to protect the labile vaccines from degradation and enhance adsorption (page 699). The commercially purchased poly-(L-lactide) has a molecular weight of 100 kDa and used in a modified double emulsion solvent evaporation method (page 699). Microencapsulation of the subunits comprised both the V and F1 antigen wherein the microspheres were later lyophilized (page 699). Eyles et al., also teach that the intra-nasal route is an attractive route for mucosal delivery (page 699).

It is noted that Eyles et al., teach the use of such microparticles and/or spheres and the associated chemical compounds and the claimed ratios. No more than routine skill is required to change the concentration or ratio of well known compositions and such changes do not impart patentability to the composition.

Therefore, it would have been prima facie obvious at the time of applicants' invention to have used the known trimethyl chitosan pharmaceutical compositons as taught by Kotze et al., and modify the composition to include the combination of the V and F1 antigen of *Yersinia pestis* comprised within particle forming spheres as taught by Eyles et al., because Eyles et al., teach that it is well known in the art to make and use phamaceutical compostions that protect labile vaccines from degradation and enhance adsorption. Moreover, no more than routine skill would have been required to the modify the well known composition which is known to be useful as a constituent in

microspheres and has the ability to act as a coating material for liposomes since the modification merely incorporates using antigenic products and well known microsphere encapsulation for the well known purpose of inducing immunity in a subject. One would have a reasonable expectation of success since no more than routine skill would have been required to use commerically available microspheres containing the antigen combination when the art teaches the success and usefulness of using both the protective F1 and V antigens.

8. Claims 1, 3-6, 11-12, 16, 18-21 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kotze et al., (International J. of Pharm., 1997) in view of Illum (WO 97/20576 published June, 1997).

The claims are drawn to the pharmaceutical composition comprising trimethyl chitosan, biologically active agents capable of generating a protective immune response against tetanus or diphtheria and microsphere particles. Kotze et al., has been discussed above as teaching a composition comprising trimethyl chitosan however Kotze et al., do not discuss compositions further comprising biologically active agents capable of generating an protective immune response against tetanus or diphtheria and microsphere particles.

Illum teach vaccine compositions for intranasal administration wherein the compositions comprise one or more antigens, an effective adjuvant and chitosan (page 1, lines 1-6). Certain adjuvants have shown that when co-administered with vaccine antigens they further boost the effectiveness of the vaccine compositions by stimulating

the immune response (page 2, lines 17-20). Chitosans are known to be mucosal absorption enhancers and upon intranasal co-administration, chitosan enhances the immune response of antigens and provide an enhanced effect upon the host (page 3, lines 1-6). The invention also teaches that vaccines are typically administered parenterally via injections (page 1 lines 20-21). Suitable antigens include tetanus antigens, such as the tetanus toxoid and diptheria antigens, such as the diphtheria toxoid (pages 4-5, lines 23-1). The intranasal compositions can be formulated in the form of microspheres (page 6, lines 22-24). Thus the composition comprises a formulation using microparticles or microspheres along with the chitosan and biologically active agents just as claimed. Thus the pharmaceutical compositions of Illum comprising biologically active agents or antigens which are capable of generating a protective immune response in an animal along with the polycationic carbohydrate chitosan.

Therefore, it would have been prima facie obvious at the time of applicants' invention to have used the known trimethyl chitosan compositon as taught by Kotze et al., and modify the compositions to include the biologically active antigen agents capable of generating a protective immune response and providing the compositions in a microparticle formulation as taught by both Kotze et al., and Illum. One would have a reasonable expectation of success in having a trimethly chitosan composition which already has well known properties such as at low cost, highly biocompatible, biodegradable, the ease of being chemically modified, gel-forming properties and being useful in microspheres systems and combining it antigens in particle formation to

achieve sustained release and enhanced mucosal absorption. Moreover, no more than routine skill would have been required to the modify the well known composition since the modification merely incorporates using encapsulation of antigenic material within microparticulate polymeric carriers to protect labile vaccines from degradation and enhance adsorption.

9. Claims 1, 3- 6, 11-12, 20-22 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kotze et al., (International J. of Pharm., 1997) in view of Duncan et al., (WO 94/20070 published September 1994).

The claims are drawn to the pharmaceutical composition comprising trimethyl chitosan, biologically active agents capable of generating a protective immune response, microsphere particles and cationic pluronics. Kotze et al., has been discussed above as teaching a composition comprising trimethyl chitosan however Kotze et al., do not discuss compositions further comprising biologically active agents, microsphere particles and cationic pluronics.

Duncan et al., teach compositions comprising: i) biologically active agents, such as immunogens or antigens at pages 4-5 para.1, ii) an adjuvant chemical having adjuvant properties wherein the adjuvants include Pluronic^{TM} block copolymers, polycations such as DEAE-4 dextran and polyarnithine at pages 9-10, para. 1; and iii) an acceptable carrier such as a mucoadhesive at page 6, para.1. Duncan et al., further teach that an enhancement in the immune response is observed when the adjuvant is combined with the immunogen and muchoadhesive (pages 10-11, para.2).

The antigens are more immunogenic when they are incorporated into the polymeric microparticles, nanoparticles or liposomes (page 2, para.4).

Therefore, it would have been prima facie obvious at the time of applicants' invention to have used the known trimethyl chitosan compositon as taught by Kotze et al., and modify the compositions to include the biologically active antigen and adjuvant agents capable of generating a protective immune response and providing the compositions in a microparticle formulation as taught by Duncan et al. One would have a reasonable expectation of success in having a trimethly chitosan compositon, a muchoadhesive which already has well known properties such as low cost, high biocompatible, being biodegradable, easy chemical modification, having gel-forming properties and being useful in microspheres systems and combining it with antigens and cationic pluronic adjuvants in particle formation to achieve enhanced mucosal absorption. Moreover, no more than routine skill would have been required to the modify the well known composition since the modification merely incorporates using antigenic and adjuvant material within microparticulate polymeric carriers to enhance adsorption.

Response to Arguments

10. Applicants' urge that Kotze et al., is silent to the use of trimethyl chitosan (TMC) as an immunostimmulant. And that neither Kotze et al., nor Illum use TMC as an immunostimulant. The fact that the art discloses that the composition may be used as for a different use than as an immunostimulant does not distinguish the instant claims over the art. A known or obvious composition does not become patentable simply

because it has been described as having a different use, especially when that use is not claimed. Therefore contrary to applicants' argument that they are claiming a novel use of two specific chitosans; the prior art does not teach away from the instant claims, since the prior art teaches compositions comprises exactly the same components as the instant claims. Thus the additional or other uses are irrelevant.

Applicants' assert that the instant composition has the feature of having the antigen and adjuvant distributed throughout the composition. However in response to applicant's argument, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. Moreover, the claim does not include any additional components which the prior art does not have. Therefore applicants' argument is not persuasive and several of the same references have been used in the new rejections.

Conclusion

11. No claims allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines

October 7, 2005